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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,474	07/14/2004	Stephen Neidle	1090-102	2378

23117 7590 03/14/2006

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EXAMINER	
RAHMANI, NILOOFAR	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 03/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/501,474	NEIDLE ET AL.	
	Examiner	Art Unit	
	Niloofar Rahmani	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *78-140* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78-80,82,84-88,90,112,114-118,120,122,123,129,130 and 132-140* is/are rejected.

7)☒ Claim(s) *81,83,89,91-111,113,119,121,124-128 and 131* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The office action of 11/18/2005 has been vacated.

Claims 78-140 are currently pending and claims 1-77 are cancelled in the instant application.

Priority

2. This application is a 371 of PCT/GB03/00102, filed on 01/14/2003, which claims the priority of UNITED STATES OF AMERICA 60347899, filed on 01/15/2002.

3. *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 78, 136-137 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 78, 136 are rejected because the term "hydrates" is confusing. What does it mean by hydrates? It is recommended to correct to hydrates.

Claim 137 is rejected because the term "composition" is ambiguous. Are they claiming "pharmaceutical composition"? If they claiming pharmaceutical composition, then "therapeutically effective amount" be incorporated in the claims.

Claims 112-113 are rejected because the term " R" is vague and unclear. Does it mean R^{N2} or R_1? Correction is required.

Claims 110-114 are rejected because the term "2', 3', 4', 5', 6'" are ambiguous. Are they the substituents? Inserting the definition into the claims would correct the matter.

Claims 87, 114-118, 120, 122-123, 129 are rejected because the term "NR^1R^2, NR^3R^4" is undefined. Correction is required.

Claims 134-135 are rejected because the term " R^N" is vague and unclear. Does it mean R^{N1} or R^{N2}? Correction is required.

4. *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 138-140 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 78, 136 lack description of the claims i.e. " hydrates". Hydrate is unpredictable because there are different hydrates. There are ½ hydrate, 3 hydrates, or ¾ hydrate, etc. Therefore, the specification lacks description of "hydrates".

Claim 138 lacks description of the claim i.e. " inhibiting telomerase in vitro or in vivo". On page 106, Table 1 of the specification, applicant has example

telomerase inhibitory activity and cytotoxicity for salts. However, applicant has not shown the nexus for inhibition telomerase in vitro or in vivo and treating or preventing any and all known diseases. In addition, what diseases are treatable or preventable by inhibiting telomerase? Therefore, the specification lacks description of " treating or preventing diseases associated with inhibiting telomerase".

5. Claims 139-140 lack description of the claim i.e. " regulating cell proliferation in vitro or in vivo". Applicant has not shown the nexus for regulation cell proliferation and regulating any and all known diseases or treatment of a proliferative condition. In addition, what diseases are regulated by cell proliferation? Therefore, the specification lacks description of "regulating cell proliferation".

6. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 138 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims.
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,
5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The instant invention is drawn to method of inhibiting telomerase in vitro or in vivo, comprising contacting a cell with an effective amount of a compound according to claim 78.

The state of the prior art: "It is clear that telomere maintenance is important to all dividing cells, including cancer cells. It is appears that the activation of the enzyme telomerase is the major mechanism by which these cells maintain their telomerase. The proposal that a critical step in the process of the malignant

transformation of cells is the upregulation of expression of telomerase has made this enzyme a potentially useful prognostic and diagnostic marker for cancer, as well as a new target for therapeutic intervention for the treatment of patients with cancer. Inhibition of the telomerase enzyme would result of tumorcell growth or regression of the tumor due to the effects of sustained telomere erosion." (Oncogene, Vol. 19, pages 6632-6641).

" Telomerase is critical for tumor cell immortalization and is a novel target for cancer chemotherapy. We conclude that telomerase activity does not account for the differential chemosensitivity of human glioma cells and that penclomedine kills glioma cells via a telomerase-independent pathway." (European Journal of Pharmacology, Vol. 407, pages 27-37).

The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seeming high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is

necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the compounds of formula of claim 78 would be used for inhibiting telomerase.

Amount of guidance/working examples: On page 106, Table 1 of the specification, applicant has example telomerase inhibitory activity and cytotoxicity for salts. However, applicant has not guidance or examples for inhibiting telomerase in vivo, comprising a cell with an effective amount of a compound according to claim 78. The specification does not seem to enable the correlation between a compound of claim 78 and the inhibiting telomerase in vivo.

The breadth of the claims: The breadth of claims is drawn to inhibiting telomerase, comprising contacting a cell with an effective amount of a compound according to claim 78.

The quantity of undue experimentation needed: Since the guidance and teaching provided by the specification is insufficient for inhibiting telomerase, one of ordinary skill in the art, even with high level of skill, is unable to use the instant compounds as claimed without undue experimentation.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the

desired pharmacological activity and which diseases would benefit from this activity.

Taking all of the above into consideration, it is not seen where the instant claim 138, for inhibiting telomerase, have been enabled by the instant specification.

7. Claims 139-140 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims.
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,

5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The instant invention is drawn to method of regulating cell proliferation in vitro or in vivo, comprising contacting a cell with an effective amount of a compound according to claim 78.

The state of the prior art: " Telomerase is critical for tumor cell immortalization and is a novel target for cancer chemotherapy. We conclude that telomerase activity does not account for the differential chemosensitivity of human glioma cells and that penclomedine kills glioma cells via a telomerase-independent pathway." (European Journal of Pharmacology, Vol. 407, pages 27-37).

The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seeming high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is

necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the compounds of formula of claim 78 would be used for regulating cell proliferation in vitro or vivo.

Amount of guidance/working examples: Applicant has not guidance or examples for regulating cell proliferation, comprising contacting a cell with an effective amount of a compound according to claim 78. The specification does not seem to enable the correlation between a compound of claim 78 and the regulating cell proliferation and treatment of a proliferative condition.

The breadth of the claims: The breadth of claims is drawn to regulating cell proliferation in vitro or vivo or the treatment of a proliferative condition, comprising contacting a cell with an effective amount of a compound according to claim 78.

The quantity of undue experimentation needed: Since the guidance and teaching provided by the specification is insufficient for regulating cell proliferation, one of ordinary skill in the art, even with high level of skill, is unable to use the instant compounds as claimed without undue experimentation.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the

desired pharmacological activity and which diseases would benefit from this activity.

Taking all of the above into consideration, it is not seen where the instant claim 139-140, for regulating cell proliferation, have been enabled by the instant specification.

8. *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 78, 80, 82, 84-86, 88, 112, 130, 132-133 are rejected under 35 U.S.C. 102(b) as being anticipated by Gamage et al., " Synthesis and in vitro Evaluation of 9-Anilino-3,6-diaminoacridines Active Against a Multidrug-Resistant Strain of the Malaria Parasite Plasmodium falciparum", Journal of medicinal Chemistry, vol. 37, pages 1486-1494. Gamage et al. disclosed the instant claimed product on page 1489, table 1, where in X is 3,6-diNMe_2. Therefore, the instant claim is anticipated by Gamage et al.

9. *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 78, 79, 82, 84-86, 88, 130, 132, 133 are rejected under 103(a) as being unpatentable over Read et al., " Structure-based design of selective and potent G quadruplex-mediated telomerase inhibitors", Proceedings of the National Academy of Sciences of the United States of America, vol. 98, pages 4844-4849 in view of Gamage et al.," Synthesis and in vitro Evaluation of 9-Anilino-3,6-diaminoacridines Active Against a Multidrug-Resistant Strain of the Malaria Parasite Plasmodium falciparum", Journal of medicinal Chemistry, vol. 37, pages 1486-1494.

Determination of the scope and content of the prior art (MPEP §2141.01)

Read et al. on the page 4846, figure 2, lines 2 and 3 disclosed analogous compounds where in J^1 and J^2 are both NH_2 and K=O in the instant application.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claim and the prior art compound is that the instant claim replaces one H of the prior art compound with a methyl.

The Gamage et al. teaches that both NH_2 and methylate amino are optional choices for such compounds.

Finding of prima facia obviousness-rational and motivation (MPEP §2142.2143)

One having ordinary skill in the art would be motivated to modify the compounds of Read et al. with a conventional alternative conversion step by adding a methyl group to NH_2 to obtain the instant compound. Because Gamage et al. teaches that both NH_2 and methylate amino are optional choices for such compounds.

10. Claims 78, 79, 82, 84, 85, 86, 88, 130, 132, 133 are rejected under 103(a) as being unpatentable over McConnaughie et al., " Novel Acridine-Triazenes as Prototype Combilexins:Synthesis, DNA Binding, and Biological Activity", Journal of medicinal Chemistry, vol. 38, pages 3488-501 in view of Gamage et al., " Synthesis and in vitro Evaluation of 9-Anilino-3,6-diaminoacridines Active Against a Multidrug-Resistant Strain of the Malaria Parasite Plasmodium falciparum", Journal of medicinal Chemistry, vol. 37, pages 1486-1494.

Determination of the scope and content of the prior art (MPEP §2141.01)

McConnaughie et al. on the page 3491, scheme 3 disclosed analogous compounds where in in J^1 and J^2 are both NH_2 and K=O.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claim and the prior art compound is that the instant claim replaces one H of the prior art compound with a methyl. The Gamage et al. teaches that both NH_2 and methylate amino are optional choices for such compounds.

Finding of prima facia obviousness-rational and motivation (MPEP §2142.2143)

One having ordinary skill in the art would be motivated to modify the compounds of McConnaughie et al. with a conventional alternative conversion step by adding a methyl group to NH_2 to obtain the instant compound. Because Gamage et al. teaches that both NH_2 and methylate amino are optional choices for such compounds.

11. ***Claim Objections***

Claims 81, 83, 89, 91-111, 113, 119, 121, 124-128, 131 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The closest art is Gamage et al., however Gamage et al. teaches 3, and 6 substituents instead of 7, and 2 for J^1 and J^2. There is no reason to modify these changes. Therefore, the claims are free of prior art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NILOOFAR RAHMANI
02/28/2006
NR

D. MARGARET SEAMAN
PRIMARY EXAMINER
GROUP 1625